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Functionalization of BINOL and application in the homo- and heterogeneous enantioselective epoxidation of α,β-unsaturated ketones

Moulay Youness El Kadiri, Eric Framery, Bruno Andrioletti *

Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (Equipe CASYEN), UMR-CNRS 5246, Université Claude Bernard Lyon 1, Bâtiment Curien (CPE), 43 Boulevard du 11 novembre 1918, F-69622 Villeurbanne Cedex, France

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ABSTRACT

The selective functionalization of BINOL derivatives with 3-(dimethylamino)prop-1-yn-1-yl is described. The corresponding La and Yb complexes were evaluated toward the epoxidation of α,β-unsaturated ketones. The Yb-complexes display the highest catalytic activity and selectivity, affording the expected chiral epoxides in quantitative yields and up to 90% ee in homogeneous conditions, and 93% ee when supported on silica gel.

The asymmetric epoxidation of olefins is one of the most versatile but challenging reactions in modern organic chemistry. Indeed, it is very valuable for affording chiral intermediates commonly used for the synthesis of a large variety of natural products and pharmaceuticals.[1] In 1980, Sharpless et al. reported the stoichiometric asymmetric epoxidation of allylic alcohols,[2] further optimized to a catalytic version thanks to the addition of molecular sieves (MS).[3] About ten years later, the groups of Jacobsen,[4] Katsuki,[5] and Mukaiyama[6] developed the asymmetric epoxidation of unfunctionalized olefins using salen ligands. Ultimately, the more challenging asymmetric epoxidation of electron-deficient olefins was investigated. The first results in this field appeared at the end of the 90s in the literature. During the course of our studies on epoxidation,[7] we and others[8] have been interested in the chiral metal peroxide catalytic system pioneered by Weitz and Scheffer.[9] Considering the moderate yields and enantioselectivities obtained when using the chiral platinum/diphosphine/peroxide complex,[10] a number of metals, including zinc associated to (1*R*,2*R*)-*N*-methylpseudoephedrine[11] and magnesium combined with (+)-diethyl tartrate,[12] were proposed, affording excellent results.

By the same period of time, Shibasaki et al.[13] disclosed an alternative based on lanthanides. The catalytic system involved lanthanum or ytterbium, (*R*)- or (*S*)-2,2′-dihydroxy-1,1′-binaphthalene (BINOL), *tert*-butyl hydroperoxide (TBHP) or cumene hydroperoxide (CMHP), and 4 Å MS in THF. Using the latter system, the enantioselective epoxidation of unsaturated ketones was greatly improved, affording up to 98% ee, with the addition of a small amount of phosphine- or arsine oxide (15 mol %) as additive.[14] When ytterbium was used, the activity was further improved by the addition of water (4.5 equiv relative to Yb).[15] Consequently, these lanthanide/BINOL catalysts appeared as very efficient catalysts both in terms of reactivity and enantioselectivity for the epoxidation of α,β-unsaturated *N*-acylimidazoles,[16] amides,[17] and *N*-acylpyrroles as carboxylic acid derivatives,[18] and moderately selective for ester derivatives.[19]

BINOL is a robust and versatile chiral reagent, easily functionalized.[20] However, it is worth reminding that the introduction of substituents on the BINOL skeleton might have a profound impact on the activity and enantioselectivity of the catalyst due to the modified electronic and steric properties. As far as we know, few reports have discussed this problem in the asymmetric epoxidation of α,β-unsaturated ketones. Noticeably, de Vries et al. have reported on the advantages of the 6,6′-dibromo- or 6,6′-diphenyl-BINOL on the epoxidation of α,β-enones.[21] Correlatively, several groups have proposed to functionalize BINOL with ammonium salts in order to use the catalysts in asymmetric phase-transfer reactions.[22] However, to the best of our knowledge, only one example of ammonium salt derived from BINOL has been reported in the case of asymmetric phase-transfer epoxidation of chalcone with alkaline hydrogen peroxide.[23] In addition, the phase-transfer nucleophilic epoxidation of α,β-enones is based mainly on the use of ammonium salts derived from cinchonine or quinidine derivatives,[24] even if two examples of ammonium salts derived from binaphthyl were also reported.[25]

* Corresponding author. Tel.: +33 (0) 472 446 264; fax: +33 (0) 472 448 160.
E-mail address: bruno.andrioletti@univ-lyon1.fr (B. Andrioletti).

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Based on the limited number of precedents described in the literature and on our experience in BINOL modification[26] and catalyst recycling,[27] we decided to undertake the synthesis of the two new ligands **1** and **2** (Fig. 1), designed for allowing an easy, non-covalent grafting on a polar silica-gel support. **1** and **2** derive from BINOL and display one or two *N,N*-dimethyl-2-propynylamine functions on the 6, or 6,6′ positions of BINOL. The catalytic performances of the two new ligands were evaluated toward the catalytic asymmetric epoxidation of two α,β-unsaturated ketones (chalcone and benzalacetone) under homo- and heterogeneous conditions, including phase-transfer catalysis.

The 6- and 6′-positions of BINOL are equally activated toward electrophilic aromatic substitution.[28] However, it has been reported that the introduction of a bulky pivaloyl group on the 2-position alters the electronic character of the naphthalene units allowing a desymmetrization of the 6- and 6′-positions.[29] Thus, we decided to use this strategy to prepare the (*R*)-6-[3-(dimethylamino)prop-1-yn-1yl]-2,2′-dihydroxy-1,1′-binaphthalene ligand **1** (Scheme 1). Compound **3** was prepared according to literature protocols,[29,30] and was reacted with *N,N*-dimethyl-2-propynylamine under classical Pd-catalyzed Sonogashira coupling conditions, to give, after deprotection under basic condition, the expected ligand **1** in 85% yield after purification.

In parallel, we investigated the synthesis of (*R*)-6,6′-bis[3-(dimethylamino)prop-1-yn-1yl]-2,2′-dihydroxy-1,1′-binaphthalene ligand **2** (Scheme 2). Firstly, we tried the direct Pd-catalyzed Sonogashira coupling between the dibromo-BINOL derivative **4**,[31] and *N,N*-dimethyl-2-propynylamine. If the ^{1}H NMR spectra of the crude material confirmed that the expected coupling compound **2** had been formed as the major product, its isolation by column chromatography remained unsuccessful, because of the strong interaction between **2** and silica-gel. To prevent this issue, we protected the hydroxyl groups as methoxy function after bromination of the 6,6′-positions of the BINOL. Thus, a direct methylation of compound **4** with NaH and methyliodide afforded the corresponding protected derivative **5a** in quantitative yield.[32] Following, the Sonogashira-coupling was performed, affording product **6a** in 50% yield after purification on silica gel. Unfortunately, the deprotection of the methoxy groups using the classical BBr_3 method,[33] remained elusive because of the presence of the dimethylamines. For this reason, we decided to protect the hydroxyl groups as –OMOM functions that can be cleaved under mild acidic conditions. Thus, the protected derivative **5b** was isolated in quantitative yield.[34] Interestingly, in comparison with the corresponding methoxy derivative **5a**, compound **5b** displayed a higher reactivity toward the Sonogashira coupling as the bis-dimethylamino derivative **6b** was isolated after purification on silica gel in 85% yield. An acidic treatment followed by a careful adjustment of the pH using a saturated aqueous solution of $NaHCO_3$, afforded ligand **2** in quantitative yield.

In an attempt to evaluate the catalytic performance of ligands **1** and **2**, we examined the asymmetric epoxidation of α,β-unsaturated ketones such as chalcone and benzalacetone. Using the epoxidation conditions pioneered by Shibasaki et al.,[14b] the asymmetric epoxidation of the afore-mentioned olefins was performed in THF

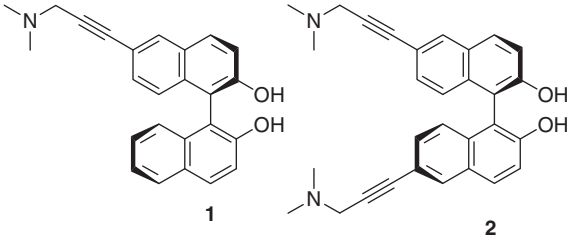
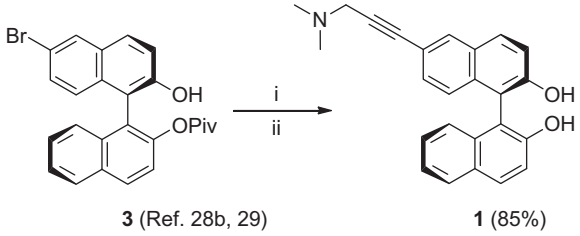
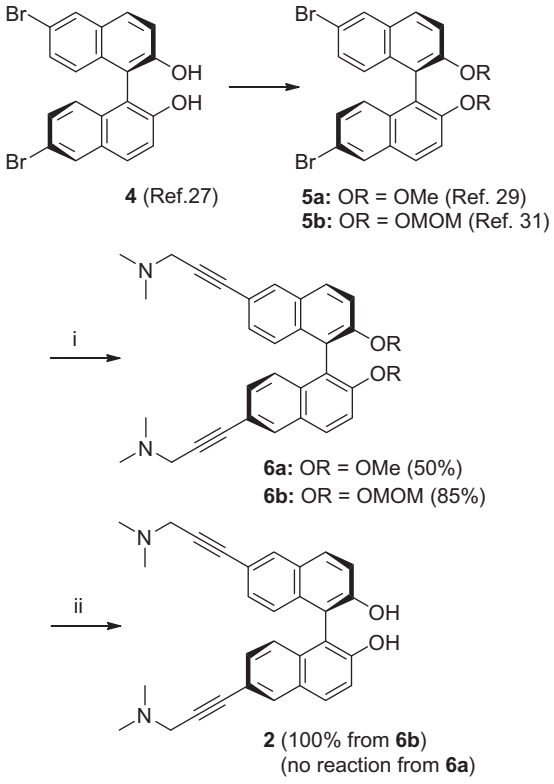


Figure 1. Target BINOL-based ligands.



i: $Me_2NCH_2C{\equiv}CH$, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 75°C, 5 days
ii: KOH, MeOH - THF, r.t., 15 h

Scheme 1. Synthesis of the (*R*)-6-monosubstituted-BINOL ligand **1**.



i: $Me_2NCH_2C{\equiv}CH$, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 75°C; 5 days
ii for **6a** BBr_3, r.t.
for **6b** HCl (37%), MeOH, r.t.; 15h, pH-neutralization with $NaHCO_3$

Scheme 2. Synthesis of the (*R*)-6,6′-disubstituted-BINOL ligand **2**.

(0.66 M), using 10 mol % of catalyst prepared in situ from La(O*i*Pr)$_3$ or Yb(O*i*Pr)$_3$ and ligand **1** or **2** in a 1:1 ratio and by adding 60 mol % of triphenylphosphine oxide as additive, 2 equiv of *tert*-butyl hydroperoxide (TBHP) and dried 4 Å MS (800 mg per mmole of enone). The reactions were performed at 30 °C. The results obtained are gathered in Table 1.

In order to test our catalytic reactions and compare our results with Shibasaki's,[14b] we decided to run a reference reaction using La/(*R*)-BINOL and chalcone (R = Ph) as a substrate. After 2 days, a full conversion was obtained, and a medium enantiomeric excess of 57% was measured (Table 1, entry 3). The difference with results reported in the literature (Y = 99%, ee = 96%) may be attributed to the source of lanthanide salt or the water content (amount of MS) that is known to be critical for this type of reactions. A reference reaction with the Yb/(*R*)-BINOL catalyst was also performed (Table 1, entry 4). In the latter case, the enantiomeric excess reached 81%. Replacing (*R*)-BINOL with ligand **1** or **2** also afforded the best enantioselectivities when Yb was used at the expense of